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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/444,790	05/19/1995	MANFRED BROCKHAUS	9189	5612

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AMGEN INC.
LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119.

EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
10/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.**	**Applicant(s)**	
	08/444,790	BROCKHAUS ET AL.	
	Examiner	**Art Unit**	
	Zachary C. Howard	1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 August 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *6* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *23 August 2007*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☒ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *62,102,103,105-107,110,111,113,114,119-121,123-137 and 140-144*.
   Claim(s) withdrawn from consideration: *139*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☒ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☒ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). 3/5/2007
13. ☐ Other: _____.

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646

Continuation of 3. NOTE: The proposed amendments filed after a final rejection, but prior to the date of filing a brief, will not be entered because they raise the issue of new matter.

In the proposed amendments, Applicants have amended "(TNF) binding soluble fragment" to "extracellular region" in each of independent claims 1, 127, 140 and 141. In the response (pg 8), Applicants argue support for the phrase "extracellular region" exists on pages 37 and 40 of the specification as originally filed. However, as Applicants admit, the references on these pages describe only the extracellular part or region of the 55 kD receptor, which is a protein with a different sequence than the 75 kD receptor recited in the pending claims. Applicants further argue that "Applicants disclose, at almost every instance, that the exemplary embodiments relate to both of the 55 kD and 75 kD TNF binding proteins that are the subject of the application". Applicants cite pages 9, line 19 through page 10, line 10 and page 14, lines 32-36. The Examiner has reviewed these pages and finds no disclosure of the extracelluar region of a 75 kD protein. Page 10 of the specification discloses that one example of a soluble protein derived from the 55 kD receptor is a particular nucleotide sequence (residues -185 or -14 to 633), which encodes the entire extracellular region. However, with respect to the 75 kD protein, there is no corresponding exemplary nucleotide sequence that corresponds to "the extracellular region". There is only a description that sequences that contain "the partial cDNA sequences of Figure 4 are preferred" and "DNA sequences which code for insoluble as well as soluble fractions of TNF-binding proteins having an apparent molecule weight of 65 kD/75 kD". As such there is no conception in the specification as originally filed that one example of a soluble 75 kD protein fragment is "the extracellular domain" of a 75 kD TNF receptor protein. Furthermore, the specification does not even disclose the specific region that is the extracellular region of the protein shown in Figure 4. Page 14, lines 32-36, states "On the basis of the thus-determined sequences and of the already known sequences for certain receptors, those partial sequences that which code for soluble TNF-BP fragments can be determined and cut out from the complete sequence using known methods". This statement indicates that soluble fragments of the sequence of Figure 4 are part of the invention, but provides no indication that "the extracellular domain" is one specific example of a soluble fragment of a 75 kD TNF receptor protein.

Applicants further argue that entry of the amendment is requested because it responds to new issues raised in the Action, which Applicants had not previously had the opportunity to respond to. Applicants point to the statement in the previous Office Action that "the term 'insoluble human TNF receptor' does not limit the receptor to any particular naturally occurring human receptor, but includes allelic variants as well as artificial receptors with one or more amino acid mutations to the sequence of the insoluble human TNF receptor". Applicants argue that this is a newly raised interpretation of the term "human" that was not raised in the prior office action or during the interview when applicants discussed the meaning of the term. However, the phrase "insoluble human TNF receptor" was a new claim limitation (made in conjunction with a change in referenced sequence from SEQ ID NO: 4 to SEQ ID NO: 10), and the comment in the 2/23/07 Final Rejection was made in response to Applicants' arguments that "human" limited the claim to naturally occurring sequences; therefore, the action was properly made final. Furthermore, in the previous Non-Final Office Action (mailed 4/3/06), the rejection stated "the claimed protein comprises any soluble fragment of TNFR2 that comprises any fragment of SEQ ID NO: 4".

In conclusion, introduction of the limitation of "the extracellular region" (as opposed to the TNF binding soluble fragment) is new matter with respect to the 75 kD protein. This new matter would require a new rejection under 112, 1st paragraph for lack of written description of this matter in the specification as originally filed. Therefore, the amendment to the claims has not been entered, and the pending claims remain those considered in the previous Office Action, and the rejections are maintained for the reasons set forth previously.

It is noted that the amended submitted by Applicants on 8/6/07 indicates that the status of claim 139 is "previously presented". However, as indicated at pg 2-3 of the 2/23/07 Office Action, claim 139 (which was newly added at that time) was withdrawn from consideration as being directed to a non-elected invention. While the current claim amendments have not been entered, in any future claim amendments Applicants should indicate claim 139 as "withdrawn".

Applicants have submitted (on 8/6/07) a certified copy of European Patent Application Number 90116702.2 (now Patent Number EP 0147563), a Second Declaration of Stewart Lyman under 37 C.F.R. § 1.132 which includes (as Appendix B) an English translation of said EPO application; and a new Application Data Sheet that identifies said EPO application in the Foreign Priority Information section. Each of these submissions is entered. In view of these submissions, the instant application merits priority to the 8/31/1990 filing date of 90116707.2.

Status of the Claims

Claims 62,102,103,105-107,110,111,113,114,119-121 and 123-137 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was set forth previously and maintained at pg 5-13 of the 2/23/07 Office Action.

At pg 7 of the 8/6/07 after final response, Applicants discuss "Submission of Lyman Declaration". Applicants submit (on 8/6/07) a Declaration Under 37 C.F.R. § 1.132 of Stewart Lyman, Ph. D. Applicants submit this Declaration to respond to "the Examiner's interpretation of the specification, including the specification's citation of Smith 1990 at page 10". This Declaration has been entered, as noted above. At pg 9 of the response, Applicants submit that "Dr. Lyman's conclusion upon reviewing the specification, including these cited portions, is that one skilled in the art at the time would have understood that the application contemplated that the entire extracellular region of p75 TNFR was a specific example of a soluble fragment of a TNF binding protein".

This Declaration has been fully considered but is not sufficient to overcome the rejection of the claims for the following reasons.

The statements made at pages in paragraphs 1-7 of the Declaration are not disputed.

In paragraph 8, the Declaration states, "One of skill in the art as of September 10, 1990 would have understood that the application used the term "soluble fragment" to mean a fragment of the full length receptor missing the intracellular and transmembrane regions. Applicants point to page 3, lines 14-16 of the specification, which states "Moreover, the TNF-binding proteins described in the state of the art are soluble, i.e., non-membrane bound, TNF-BP". The Declaration states that, "[t]hus, the term "soluble fragment" refers to the extracellular domain of a TNF receptor or fragments of this domain". The Declaration further states, "one of skill in would have expected that the extracellular region of TNFR would bind to TNF". In paragraph 9, the Declaration states that Applicants the applications use of the term soluble fragment is consistent with how the term was used in the art at the time.

These statements in the Declaration have been fully considered but are not sufficient to overcome the rejection. The examiner does not dispute that "soluble fragments" can refer either to the extracellular domain of a TNF receptor or to fragments of this domain, or that this usage is consistent with how it was used in the art at the time of filing. However, as stated the term includes "fragments" of the extracellular domain. The instant specification provides only a partial sequence of the extracellular domain (SEQ ID NO: 4; which is missing residues critical for TNF binding), and only refers to the invention as including soluble fragments taken from this sequence. Therefore, the soluble fragments described in the instant application are only fragments of the extracellular domain. Therefore, the reference to "soluble fragments" in the instant specification does not provide a written description of the full-length extracellular domain, which is necessary to construct a soluble fragment with TNF-binding properties. The Examiner does not dispute that the skilled artisan would have expected the full-length extracellular region of TNFR would bind to TNF. However, for the reasons set forth previously and maintained herein, the specification does not provide a description of such full-length sequences, nor indicate that such sequences are part of the invention.

Paragraphs 10 and 12 of the Declaration argue that the skilled artisan would have known that the application contemplated the extracellular region of the TNF binding protein as a particular, specifically described example of a soluble fragment (page 10, lines 19-23 of the specification) and that the application further specifically contemplated use of the extracellular region of a TNF binding protein in an Ig fusion protein (Example 11 in the specification). In Paragraph 17, the Declaration points to page 20, lines 27-30 and states that any teachings made with regard to the 55 kD TNFR should apply equally to the 75 KD protein.

These statements in the Declaration have been fully considered but are not sufficient to overcome the rejection. Page 10, lines 19-23 and Example 11 provide teachings that are directed solely to the 55 kD protein, and there are no corresponding teachings directed to the 75 kD protein. The teachings on page 10, directed to the 75/65 kD protein only refer to proteins that contain the partial sequence shown in Figure 4, and soluble fragments thereof. Nowhere does the specification provide the full-length extracellular sequence of the 75 kD protein, or indicate that this sequence is part of the invention. Page 20, lines 27-30 of the specification merely states that the invention has been described in general terms and that details that are provided are not intended to limit the invention. Such a statement is not sufficient to direct the skilled artisan to the particular invention that is now claimed. In Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 1326, 56 USPQ2d 1481, 1486 (Fed Cir. 2000), the court noted that with respect to In re Ruschig 379 F.2d 990, 154 USPQ 118 (CCPA 1967) that "Ruschig makes clear that one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say "here is my invention". In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure".

The statements in paragraph 11 of the Declaration are not disputed.

In paragraph 13, the Declaration states that while the full-length sequence is not reproduced, there is a description of using fragments of such full length sequence in fusion proteins. The Declaration points to the specification page 14, lines 32-36.

These statements in the Declaration have been fully considered but are not sufficient to overcome the rejection. The statement on page 14 of the specification states, "On the basis of the thus-determined sequences of the already known sequences for certain receptors, those partial sequences which code for soluble TNF-BP fragments can be determined and cut out from the complete sequence using known methods". The statement "already known sequences for certain receptors" does not clearly specify what known sequences are referred to. This statement comes at the end of a paragraph that describes how the sequences given in Figure 1 and Figure 4 can be used to search for clones coding for TNF-BP. Thus, the already known sequences appears to refer to the sequences of Figure 1 and Figure 4. Figure 4 describes only a partial sequence of the 75 kD receptor. Thus this paragraph only suggests a potential method to determine other soluble sequences related to the sequence shown in Figure 4. There is no clear description here that these soluble fragments include the full-length sequence of the 75 kD receptor. Furthermore, the specification does not describe the sequence of the full-length extracellular domain. Adequate written description requires more than a mere statement that a compound is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fires v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co Ltd 18 USPQ2d 1016.

In paragraphs 14-16 and 18-22, the Declaration states that the citation of Smith (1990) indicates in the Application indicates that Applicants knew of Smith (1990) when the application was drafted; that the Declaration states that the skilled artisan would not ignore a publicly available sequence to complete a partial cDNA sequence, such as that found in Figure 4; and that the skilled artisan would not have interpreted the reference to Smith to refer only to deletions of the sequence of Figure 4, as set forth by the Examiner in the previous Office Action. Applicants argue that it is illogical to assume that the Smith reference must disclose a fragment of the amino acid sequence of Figure 4 because there is no soluble fragment disclosed in Smith that is a fragment of Figure 4, and that Smith must have been referenced for a nother reason. The Declaration states that the Office Action takes the sentence containing the Smith reference out of context of the entire paragraph, which is describing soluble and non-soluble fragments of TNF binding proteins, and without considering the totality of the teachings in the specification (pargraphs 20-21).

These statements in the Declaration have been fully considered but are not sufficient to overcome the rejection. It is maintained the

reference to Smith only suggests using deletions of the sequence found in Figure 4. There is no description of using the sequences in Smith to complete the sequence of Figure 4. There is no description in the instant specification that the sequence needs to be completed for TNF binding. (The relevant art cited previously shows that missing residues are critical for TNF binding). The arguments regarding the interpretation and context of the sentence containing the Smith reference have been fully considered but are not sufficient to overcome the rejection. The sentence in the specification referring to Smith clearly states, "One sequence which results from such a deletion is described for example, in Science 248, 1019-1023 (1990)". The previous sentence in the specification refers to "deletions, substitutions and additions from one or more nucleotides of the sequence given in Figure 1 or 4." Such a statement indicates that the specification only contemplates fragments that are deletions of the sequence of Figure 4, and there is no corresponding statement that the full-length extracellular domain found the sequence disclosed by Smith is part of the instant invention, even when considered in view of the entire paragraph or specification. There are no teachings in the full paragraph or the entire specification that direct the skilled artisan to the particular invention that is now claimed. In Purdue Pharma L.P. v. Faulding Inc., 230 F.3d 1320, 1326, 56 USPQ2d 1481, 1486 (Fed Cir. 2000), the court noted that with respect to In re Ruschig 379 F.2d 990, 154 USPQ 118 (CCPA 1967) that "Ruschig makes clear that one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say "here is my invention". In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure".

Paragraph 23 of the Declaraton states that the skilled artisan would not have read the application without reference to any other known invention. The Declaration points to Dembic (1990) as also teaching the full-length sequence of the 75 kD receptor.

These statements in the Declaration have been fully considered but are not sufficient to overcome the rejection. As set forth above, there is not description in the instant application of using the full-length extracellular domain of the 75 kD receptor in the claimed invention. Instead the application only points to soluble fragments derived from the partial sequence of Figure 4. Furthermore, there is no reference in the instant specification to the full-length extrcellular sequence found in Dembic. Therefore, the skilled artisan would not have view Applicants to have possession of an invention using the full-length extracellular domain at the time of filing of the application.

In summary, the Declaration has been fully considered but is not sufficient to overcome the rejection for the reasons set forth herein.

Claims 140-144 are rejected under 35 U.S.C. § 112, first paragraph, as containg subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection was set forth at pg 20-22 of the 2/23/07 Office Action.

In response to this rejection, Applicants state "Applicants submit herewith a second Budapest Declaration and request entry of such declaration pursuant to 37 C.F.R. § 1.116 to narrow the issues and place the case in better form for consideration on appeal".

Applicants' declaration titled "Declaration of Biological Culture Deposit Under Terms of the Budapest Treaty" has been entered but is not sufficient to overcome the rejection of the claims. The Declaration is sufficient to indicate that the deposit was made under terms of the Budapest treaty, and that all restrictions imposed by the depositor on availability will be removed upon granting of a patent. However, the rejection further stated:

"Even if the required information described above is provided by affidavit or declaration, the deposit will not meet the deposit requirement for the following reasons. Specifically, the deposit requirements require that the identifying information set forth in 37 C.F.R. § 1.809(d) should be added to the specification. See MPEP § 1.809. The instant specification does not contain the identifying information set forth in 37 C.F.R. § 1.809(d) for the following reasons. 37 C.F.R. § 1.809(d) states, "For each deposit made pursuant to these regulations, the specification shall contain: ... (3) A description of the deposited material sufficient to specifically identify it and to permit examination..." In the instant case, the specification was amended to recite "DNA sequences which code for insoluble (deposited on October 17, 2006 with the American Type Culture Collection under Accession No. PTA 7942) as well as soluble fractions of TNF-binding proteins having an apparent molecular weight of 65 kD/75 kD are also preferred". This statement is not sufficient to specifically identify the nature of the deposited sequence. For example, the deposited sequence could be any one or more DNA sequences which code for insoluble fractions of TNF-binding protein having an apparent molecular weight of 65 kD/75 kD. The description of the deposit is not sufficient to indicate the deposited material is a DNA sequence that was described in the specification at the time of filing. On 11/14/06, Applicants also submitted the "Third Declaration of Dr. Werner Lesslauer under 35 U.S.C. § 1.312", which indicates that the deposited material is "[a] DNA construct designated N227 containing DNA sequence which includes sequence encoding the signal sequence and the extracellular domain of human p75 tumor necrosis factor receptor (TNFR) was constructed on a date before September 10, 1990" (pg 1). However, the DNA construct designated N227 referred to by Dr. Lesslauer is not clearly disclosed in the specification as originally filed, and therefore the specification as originally filed does not teach how to make the claimed product. In view of the lack of a specific description of the deposited material, the specification does not enable the skilled artisan to make and/or use the claimed invention of claims 140-144."

Applicants' Declaration does not address this additional basis for the rejection. Therefore, the rejection is maintained for the above reasons.

The specification is objected to under 35 USC 132(a) because the amendment filed 11/14/06 introduces new matter into the disclosure. The objection was set forth at pg 19-20 of the 2/23/07 and was necessitated by Applicants' amendments.

The 8/6/07 response states, "Applicants believe that the amendments to the specification to include the deposit information (at page 10, line 11) should be entered because this amendment is not new matter". Applicants further state "Applicants intend to preserve all issues for Appeal" (pg 6).

Applicants state that the amendment is not new matter, but do not provide any arguments supporting their position. Therefore, this objection is maintained for the reasons set forth previously.

Claims 140-144 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims contain new matter. This rejection was set forth at pg 23-24 of the 2/23/07 Office Action.

With respect to this rejection, Applicants state only that "Applicants intend to preserve all issues for Appeal. Therefore, this rejection is maintained for the reasons set forth previously.

Claims 62, 102, 103, 105-107, 110, 111, 113, 114, 119-121, 125-131 and 134-137 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dembic et al (1990) in view of Capon et al (US Patent 5,116,964). This rejection was set forth previously and maintained at pg 13-19 of the 2/23/07 Office Action.

With respect to this rejection, Applicants state only that "Applicants intend to preserve all issues for Appeal. Therefore, this rejection is maintained for the reasons set forth previously.

In conclusion, the request for reconsideration has been considered but does NOT place the application in condition for allowance because the claims remain rejected for the reasons set forth above.